



Ray Paul. SP12-6796 x 40, 2013. Acrylic, latex, enamel on canvas printed with an image of myxofibrosarcoma with metastases to the artist's lung, 26" x 36".

Knowledge of transfusion complications related to HSCT can help with the early detection and treatment of patients before and after transplantation.

Transfusion Support Issues in Hematopoietic Stem Cell Transplantation

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Background: Patients receiving hematopoietic stem cell transplantation require extensive transfusion support until red blood cell and platelet engraftment occurs. Rare but predictable complications may arise when the transplanted stem cells are incompatible with the native ABO type of the patient. Immediate and delayed hemolysis is often seen.

Methods: A literature review was performed and the results from peer-reviewed papers that contained reproducible findings were integrated.

Results: A strong body of clinical evidence has developed around the common complications experienced with ABO-incompatible hematopoietic stem cell transplantation. These complications are discussed and the underlying pathophysiology is explained. General treatment options and guidelines are enumerated.

Conclusions: ABO-incompatible hematopoietic stem cell transplantations are frequently performed. Immune-related hemolysis is a commonly encountered complication; therefore, health care professionals must recognize the signs of immune-mediated hemolysis and understand the various etiologies that may drive the process.

Introduction

Hematopoietic stem cell transplantation (HSCT) is used to treat a variety of hematological and congenital diseases. The duration and specificity of transfusion support for patients receiving HSCT depends on the disease, the source of the stem cells, the preparative regimen applied prior to transplantation, and patient factors during the post-transplantation recovery period. Human leukocyte

antigen (HLA) matching remains an important predictor of success with HSCT; however, the ABO barrier is often crossed when searching for the most appropriate HLA match between donor and patient. Crossing the ABO barrier has little or no effect on overall outcomes; however, complications can arise due to antigenic incompatibility between the transplanted cells and the patient.¹ This review will discuss the transfusion support of patients receiving HSCT, common transfusion-related complications that health care professionals will likely encounter, and the measures required to safely deliver blood components.

HSCTs can be broadly divided into related allogeneic, unrelated allogeneic, and autologous transplantation. Hematopoietic progenitor cells (HPCs) for allogeneic transplantation come from 3 sources: apheresis-derived, mobilized peripheral blood pro-

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genitor cells (HPC-A), bone marrow (HPC-M), and umbilical cord (HPC-C). HPC-A is commonly used for autologous transplantation. Pediatric patients receive more HPC-M, whereas adults receive more HPC-A. Use of HPC-C is on the rise in both populations.²

Patients undergoing HSCT remain dependent on red blood cell (RBC) and platelet transfusions until engraftment of these cell lines occurs. The platelet line is considered engrafted when a patient's count is at least 20,000/ μ L after 3 consecutive days without platelet transfusion.³ RBC engraftment is more difficult to assess and may be defined by the appearance of 1% reticulocytes in the peripheral blood,⁴ or, on the day of the last RBC transfusion, with no transfusion given the following 30 days.⁵ Typically, neutrophil engraftment is defined as an absolute neutrophil count of more than 500/ μ L across 3 consecutive days.³ Engraftment is influenced by many factors, including the relationship of the donor to the patient, the stem cell source, and the dose of CD34⁺ cells in the transplantation.³ In general, engraftment time is shortest with HPC-A and greatest when HPC-C is used⁶; however, considerable patient-to-patient variability exists. One study that compared HPC-C and HPC-A noted roughly equivalent neutrophil recovery times but found a longer time to platelet and RBC engraftment for HPC-C.⁵ These prolonged engraftment times translated into higher transfusion rates for RBCs and platelets.

Pretransplantation Support

Prior to HSCT, patients may be immunocompetent or immunocompromised depending on their underlying disease. A patient who is immunocompetent (eg, aplastic anemia, hemoglobinopathies) is capable of mounting an immune response to transfusions, leading to alloimmunization against platelet antigens, HLAs present on the surface of leukocytes and platelets, or both. Antibodies against HLA contribute to delayed engraftment and graft rejection in some patient populations.^{7,8} As a result, pretransplantation transfusions in patients who are immunocompetent should be avoided because they are associated with increased graft failure rates.^{9,10} For patients who are stable, RBC transfusions can be minimized by using a hemoglobin trigger of 7 to 8 g/dL. Multiple studies have shown that using this hemoglobin threshold is at least as effective and results in similar outcomes as higher triggers unless a patient is symptomatically anemic.^{11,12}

Platelet transfusions may also be minimized by adhering to evidence-based guidelines. Using a platelet count of 10,000/ μ L as a threshold for administering platelets to a nonbleeding patient has been well established.¹³

When transfusion is required, using leukoreduced components reduces the risk of alloimmunization.¹⁴ Patients who are immunocompromised, either be-

cause of their disease or due to chemotherapy, are less likely to become sensitized to foreign antigens. Nonetheless, using leukoreduced products to minimize the risk of alloimmunization is recommended. Extra care must also be taken if the stem cell donation comes from a blood relative. In this situation, family members should not give direct blood donations because doing so may lead to alloimmunization against major and/or minor HLAs present in the transplant.¹⁵

Post-Transplantation Support

Chemotherapy regimens may be fully myeloablative or use reduced intensity conditioning to partially ablate the patient's marrow. Either regimen will cause the patient to be dependent on RBC and platelet transfusions until engraftment of those cell lines occurs. Although granulocyte progenitor cells are also destroyed, granulocyte-colony stimulating factor may be given because granulocyte transfusions are reserved for specific scenarios. The need for plasma and cryoprecipitate transfusions is less frequent because HSCT does not typically interfere with the production of coagulation factors. Refer to the article by McCullough and colleagues in this issue for more detailed information on this topic.

Although the frequency and extent of RBC and platelet transfusions are increased during the post-transplantation period, the indications for these transfusions do not change. Because no large prospective study specifically targets RBC transfusion triggers in patients undergoing HSCT, the more general guidelines from the AABB (formerly American Association of Blood Banks) may be used, which recommend adhering to a restrictive transfusion strategy (7.0–8.0 g/dL) in a stable patient who is hospitalized unless the patient is symptomatically anemic.¹⁶ Special care must be taken to transfuse irradiated RBC units alone, because the risk for transfusion-associated graft-vs-host-disease (TA-GVHD) is high in patients receiving HSCT.¹⁷ Because transplants often cross the ABO barrier, ABO compatibility may be complex in patients receiving HSCT. When the transplant creates an incompatibility issue (eg, group B transplantation into a group A patient), transfusing group O RBCs and AB plasma will be necessary (Table). The decision to switch a patient's blood type is highly variable across institutions. At my institution, if a patient is independent of RBC transfusion for 100 days and no incompatible isohemagglutinins against the new RBC phenotype can be detected in 2 consecutive blood samples, then the patient's native blood type is switched to the donor type for future transfusions.

Patients receiving HSCT undergo a period of hypoproliferative thrombocytopenia that ends when the platelet line engrafts. To support patients through this

Table. — Component Type Selection for Hematopoietic Stem Cell Transplantation Crossing the ABO Barrier

Type of Mismatch	Transplantation		Transfusion	
	Donor Type	Recipient Type	Red Blood Cell	Platelets ^a /Plasma
Major	A	O	O	A AB
	B	O	O	B AB
	AB	O	O	AB
	AB	A	A O	AB
	AB	B	B O	AB
Minor	O	A	O	A AB
	O	B	O	B AB
	O	AB	O	AB
	A	AB	A O	AB
	B	AB	B O	AB
	A	B	O	AB
Bidirectional	B	A	O	AB

^aPlatelets stored in additive solution reduce the volume of incompatible plasma transfused.

aplasia, the general triggers for platelet transfusions apply. Because the patient is a chimera of donor and native blood types, ABO-incompatibility issues may arise. Because ABO antigens are present on the surface of platelets, one must consider the ABO type of the platelets and the anti-A and anti-B antibodies present in the donor plasma in which the platelets are stored. Choosing platelet units based on plasma compatible with both the donor and patient is necessary (see Table).¹⁸ However, if a group O patient is making high-titer ABO antibodies (> 512–1024), then attention must be paid to the ABO type of the platelet unit and care must be taken to avoid group A1 platelets. Using platelet additive solution (PAS), which removes 65% of donor plasma, is an option available when the isohemagglutinin titer is a concern.¹⁹ Washing the platelet unit will also reduce or eliminate problems with lysis. However, the procedure is labor intensive and may damage the platelets. Washing can also be logistically challenging because washed platelet units become outdated after 4 hours. Refer to the article in this issue by Fletcher and colleagues for more details on this topic.

Recent studies have addressed questions of platelet dose and the comparative merits of therapeutic

compared with prophylactic platelet transfusions. One such study evaluated the effect of platelet dose on bleeding in patients with hypoproliferative thrombocytopenia.²⁰ In this study, patients were randomly assigned to receive either low-dose (1.1×10^{11} platelets), medium-dose (2.2×10^{11}), or high-dose (4.4×10^{11}) prophylactic platelet transfusions when their first morning counts were 10,000/ μ L or lower. Overall, no significant difference was seen in World Health Organization grade 2 or higher bleeding events in the 3 groups.²⁰ The low-dose group received significantly fewer platelets; however, this group also received transfusions more often. The authors concluded that using these different doses for prophylactic transfusion had no effect on the incidence of bleeding.²⁰ However, a subgroup analysis of the study data showed that pediatric patients (range, 0–18 years of age) had a significantly higher risk of grade 2 or higher bleeding than adults across all platelet dose groups.²¹ This finding was most pronounced in the pediatric autologous transplant population.²¹

Two studies examined the efficacy and safety of prophylactic compared with therapeutic platelet transfusions.^{22,23} The Trial of Prophylactic Platelet Study (TOPPS) randomly assigned patients undergoing chemotherapy or stem cell transplantation into either a therapeutic or prophylactic arm.²² Patients in the prophylactic arm received a platelet transfusion in response to a first morning platelet count of less than 10,000/ μ L, whereas the therapeutic group received platelet transfusion when clinically indicated. Results showed that the therapeutic arm used significantly fewer platelets when compared with the prophylactic group; however, patients in the therapeutic arm had higher bleeding rates, more days with bleeding, and a shorter time to the initial bleeding episode than patients in the prophylactic cohort.²² It should be noted that 70% of the patients in this study were recipients of autologous stem cell transplants, which represents a group of people who have a lower risk of bleeding than those receiving allogeneic transplantation.²⁰ When recipients of autologous transplantation were compared, the rate of bleeding was similar for both therapeutic and prophylactic groups.²²

The second large prospective trial conducted by Wandt et al²³ was performed under similar conditions as TOPPS. The researchers studied recipients of autologous stem cell transplantation and patients with acute myeloid leukemia undergoing chemotherapy. In this trial, higher rates of bleeding were seen in all patient groups receiving therapeutic platelet transfusions. In addition, the therapeutic group had 6 patients with head bleeds (2 of the 6 were fatal), whereas the prophylactic group had none.²³ As with the TOPPS trial, a significant reduction in platelet transfusions was seen in the therapeutic arm. Of note,

the similar data in the 2 studies led to different conclusions. The TOPPS group concluded that the benefit of reduced bleeding made prophylactic transfusions a preferred practice for all patients,²² whereas Wandt et al²³ made a distinction, stating that patients with acute myeloid leukemia undergoing chemotherapy should still receive prophylactic platelet transfusions but that the therapeutic strategy should become the new standard of care for patients receiving autologous stem cell transplantation.

Complications

Transfusion-related complications exist that are specific to, or more frequently seen in, the patient population receiving HSCT. Some of these complications arise when lymphocytes within the transplant are activated against the recipient, leading to TA-GVHD and passenger lymphocyte syndrome (PLS). Another complication, pure red cell aplasia (PRCA), occurs when a patient's residual antibodies attack the transplant. Standard transfusion reactions, such as allergic or febrile nonhemolytic reactions, are frequently seen in this heavily transfused patient population. Refer to the article by Marques and colleagues in this issue for a more detailed discussion of standard transfusion reactions.

Transfusion-Associated Graft-vs-Host Disease

Graft-vs-host disease is seen in patients who are severely immunocompromised and have been exposed to immunocompetent lymphocytes that recognize the body as foreign due to differences in HLAs. TA-GVHD occurs when a susceptible patient is exposed to viable lymphocytes introduced via blood transfusion. The immunocompromised recipient is incapable of rejecting or mounting an attack against the lymphocytes in the graft. Although the basic underlying etiology is similar, TA-GVHD has a different presentation and natural history when compared with conventional graft-vs-host disease. Typically, TA-GVHD presents with a maculopapular rash, enterocolitis, and pancytopenia that begin 8 to 10 days following transfusion.¹⁷ As the attacking lymphocytes target the stem cells engrafting within the bone marrow, irreversible and complete bone marrow aplasia will result. TA-GVHD develops within 21 days of transfusion and is almost always fatal.^{24,25}

Cellular blood components isolated from whole blood or collected by apheresis all contain some lymphocytes. RBC, platelet, and granulocyte units all carry risk for TA-GVHD; however, plasma and cryoprecipitate are acellular and do not pose a risk. To prevent TA-GVHD, lymphocytes within a blood component must be eliminated or disabled. Leukoreduction is not considered sufficient because the process reduces but does not completely eliminate white blood

cells.^{26,27} Frozen units may also carry risk because the lymphocytes may survive. Treating components with γ - or X-irradiation, or pathogen inactivation with UV irradiation, has been shown to be effective prophylaxis for TA-GVHD.²⁸ A dose of at least 2500 cGy into the center of a cellular blood component and 1500 cGy throughout the unit leaves lymphocytes intact but unable to proliferate.²⁹ This simple precaution prevents TA-GVHD.

Irradiation at the indicated dose appears to damage the RBC membrane.³⁰ The damage does not affect the oxygen-carrying capacity of the erythrocyte but does allow potassium to leak from the cell.³¹ The level of extracellular potassium has been shown to increase with storage time. As a result, RBCs may be stored for 28 days following irradiation.²⁹ Because platelets are not affected by irradiation, their storage time of 5 days remains unchanged.³²

All patients undergoing HSCT should receive irradiated components from the time of initiation of conditioning chemotherapy. The AABB suggests that HSCT recipients receive irradiated components for at least 1 year following transplantation,³³ although many centers continue to provide irradiated products for the life of the patient.³⁴ The British Committee for Standards in Haematology (BCSH) also recommends that irradiation begin with the initiation of conditioning chemotherapy; however, separate recommendations exist for patients receiving allogeneic compared with autologous HSCT.³⁴ The BCSH recommends that patients receiving allogeneic HSCT should continue to receive irradiated components for 6 months following transplantation or until the lymphocyte count is greater than $1 \times 10^9/L$; however, if chronic graft vs host disease is present, then irradiated products should be indefinitely given.³⁴ The BCSH states that patients receiving autologous HSCT should also receive irradiated components beginning from the time of initiation of conditioning chemotherapy, but this can revert to nonirradiated components 3 months after transplantation.³⁴ If patients receiving autologous HSCT also received total body irradiation, then the BCSH recommends extending the use of irradiated products for 6 months following transplantation.³⁴

Issues of ABO Compatibility

Crossing the ABO barrier is not considered a contraindication with HSCT. A meta-analysis found no impact on overall survival rates when comparing ABO matched and mismatched HSCTs.³⁵ Nonetheless, some complications may arise because of issues related to ABO incompatibility. The nature of the complication is often related to whether the incompatibility represents a major or minor mismatch (see Table), with a major mismatch occurring when the transplant contains RBCs incompatible with the plasma of the recipient. Conversely, a minor mismatch is present when plasma

from the donor contains isohemagglutinins against the RBCs of the recipient. Bidirectional transplantation (eg, group A transplant into group B recipient) carries both major and minor mismatches.

Major ABO Mismatches

Immediate and Delayed Hemolysis: When a major ABO mismatched transplantation is provided, immediate hemolysis may occur during the infusion. This complication is commonly seen when the HSCT is derived from bone marrow because more RBCs are present³⁶; however, RBC depletion techniques have helped eliminate this complication.³⁷ Because HSCTs derived from peripheral blood typically contain a minimal volume of RBCs (8–15 mL), clinically significant cases of immediate hemolysis have not been identified.³⁶ Most HPC-C units are RBC-depleted prior to cryopreservation, and the residual erythrocytes lyse during cryopreservation; therefore, immediate hemolysis does not occur with the transplantation of cord blood.

Preformed antibodies against non-ABO RBC antigens may remain in a recipient's peripheral circulation for many weeks following transplantation. These antibodies may cause lysis when engrafted cells begin to produce new RBCs.^{38,39} In addition, chimeric patients may develop antibodies against ABO or non-ABO RBC antigens, thus resulting in delayed hemolysis.⁴⁰

Pure Red Cell Aplasia: When recipients have isohemagglutinins specific for the ABO type of the transplant, delayed erythrocyte engraftment and PRCA may ensue. PRCA is seen frequently with group O patients receiving a group A transplantation or with bidirectional mismatches.⁴¹ The condition develops when antibodies against newly engrafted RBCs destroy erythrocyte progenitor cells in the bone marrow. This intramedullary destruction leads to severe anemia with no corresponding involvement of leukocyte or platelet cell lines. The incidence of PRCA is increased when reduced intensity conditioning regimens are used,^{42,43} likely due to residual recipient B lymphocytes, plasma cells, or both, thus producing isohemagglutinins. An increase in post-transplantation isohemagglutinin titers is also an important predisposing factor for PRCA.⁴⁴⁻⁴⁷

PRCA may spontaneously resolve,^{44,48} but treatment to reduce its duration is warranted to diminish the risk of iron overload from multiple RBC transfusions.⁴⁹ Therapy for PRCA includes bolstering the graft-vs-host effect either through withdrawal of immunosuppression⁴⁴ or with a donor infusion of leukocytes.^{42,50,51} Other treatments include erythropoietin,⁵² rituximab,^{53,54} bortezomib, or all 3 options in combination.^{43,55} Because PRCA is associated with high levels of isohemagglutinins,⁴⁴⁻⁴⁷ a direct reduction of titers by plasma exchange may be effective in some

patients.^{47,56} Although the reduction of titers before the transplantation has been attempted to prevent PRCA,^{57,58} knowing the actual effect of this approach is impossible. Some European centers use apheresis as standard care for reducing pretransplantation isohemagglutinin titers to fewer than 1:32.⁵⁹

Minor Mismatches

Passenger Lymphocyte Syndrome: If lymphocytes within the HSCT recognize the recipient RBCs as foreign, then antibodies may be produced that are specific for ABO or minor RBC antigens. PLS is seen most frequently in transplants that use a group O donor with a group A recipient,⁶⁰ and it typically presents 7 to 14 days following transplantation with an abrupt onset of hemolysis. When the passenger lymphocytes produce antibodies against the ABO system, the hemoglobin level may precipitously drop. The laboratory signs of intravascular hemolysis (ie, hemoglobinemia, hemoglobinuria, elevated level of lactate dehydrogenase) should be used to follow the course of disease. In most cases, results on a direct antiglobulin test will be positive unless all antibody-bound cells have already lysed. Hemolysis can persist as long as incompatible RBCs are present, but it typically subsides within 5 to 10 days.⁶¹ Antibodies against minor RBC antigens have been less frequently reported. In these cases, hemolysis ranges from mild to severe and may be intravascular or extravascular depending on the nature of the antibody involved.

The risk factors for PLS are similar to those seen in PRCA. A non-myeloablative-conditioning regimen carries greater risk than when full ablation is used.⁶² Because HPC-A preparations carry a greater lymphocyte load when compared with HPC-M and HPC-C collections, recipients of peripheral blood stem cells are at an increased risk for developing PLS.⁶²⁻⁶⁵ I am not aware of a PLS case reported with umbilical cord stem cell transplantation. Maintaining graft-vs-host disease prophylaxis with a T-cell inhibitor alone, such as cyclosporine A, without an accompanying B-cell inhibitor is also considered a risk factor.^{66,67}

Alloimmunization Against Minor Red Blood Cell Antigens:

The antibodies that cause PLS are temporary because they are derived from passenger lymphocytes that are not engrafted. When alloantibodies against RBCs are produced by the post-transplantation immune system, the antibodies may persist for several years,⁶⁸ and they may be produced by the engrafted cells of the immune system of the donor⁶⁹⁻⁷¹ or by the residual cells of the immune system of the recipient.^{68,72,73} The antibodies produced may be against donor RBCs, residual recipient RBCs, or, in some cases, both. The incidence of alloantibody formation against minor RBC antigens ranges from 2.1% to 3.7% in the published literature.^{74,75} These antibodies have not

been linked with significant complications.^{70,72}

Prevention of Transfusion-Transmitted Cytomegalovirus Infection: Cytomegalovirus (CMV) infection continues to be a serious complication following HSCT.⁷⁶⁻⁷⁸ Most CMV infections may be due to a reactivation of the virus from a previous infection rather than due to the acquisition of a new strain.⁷⁹ However, CMV antibody-negative persons are at risk for developing a transfusion-transmitted de novo CMV infection. To reduce this risk, one may use CMV-antibody negative blood or leukoreduced components. A large controlled trial and meta-analysis showed that leukoreduced components are as effective as antibody-negative components in the prevention of transfusion-transmitted CMV infection.^{80,81} However, a survey of AABB physician members showed wide variability in transfusion practice.⁸² Since then, 2 additional studies have been published with results that support the safety of using leukoreduced blood alone for the prevention of transfusion-transmitted CMV infection.^{83,84} These studies focused on transfusion and transmission in patients receiving allogeneic HSCT. A total of 123 patients who were CMV negative and who had received nearly 8,000 leukoreduced but unsorted blood products were analyzed. Both studies found no risk for transfusion-transmitted CMV infection. Anti-CMV immunoglobulin G was detected in some patients in both of the studies,^{83,84} but this effect was likely due to the passive transfer of antibodies during transfusions.⁸⁴ Nonetheless, the overall risk of transfusion-transmitted CMV infection in leukoreduced components is not zero. A study of blood donors in Germany found CMV DNA in 44% of newly seropositive donors and the overall prevalence of CMV DNA was 0.13% in nearly 32,000 donations.⁸⁵ The small risk of CMV-seronegative blood donors presenting in the window period of a new CMV infection has led to the suggestion that blood products for vulnerable patient groups be obtained from donors with a longstanding history of CMV-positive serology.⁸⁶ An alternative suggestion may be to screen donated blood for CMV DNA or immunoglobulin M antibodies.⁸⁶

Conclusions

Transfusion support for patients receiving stem cell transplantation depends on many factors. The source of the transplant, the conditioning regimen, and the clinical status of the patient all must enter into the decision-making process regarding the safest component. Despite advances in knowledge, technology, and screening methodologies, complications may still occur and can lead to prolonged transfusion dependence. Knowledge of these complications can help with early detection and treatment, thus reducing the number of transfusions necessary in these patients.

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